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<b>(21) International Application Number:</b> PCT/US92/05066 <b>(22) International Filing Date:</b> 23 June 1992 (23.06.92) <b>(30) Priority data:</b> 725,044                      3 July 1991 (03.07.91)                      US <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US    725,044 (CIP) Filed on    3 July 1991 (03.07.91) <b>(71) Applicant (for all designated States except US):</b> THE UP- JOHN COMPANY [US/US]; 301 Henrietta Street, Kal- amazoo, MI 49001 (US).			<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> SHEN, Robert, Wu-wei [US/US]; 5121 Maple Ridge Road, Kalamazoo, MI 49008 (US). PRICE, Jeffrey, Ellis [US/US]; 11836 Oak- land Drive, Schoolcraft, MI 49087 (US). <b>(74) Agent:</b> GAMMILL, Martha, A.; Corporate Patents & Trademarks, The Upjohn Company, Kalamazoo, MI 49001 (US). <b>(81) Designated States:</b> AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> COLESTIPOL HYDROCHLORIDE HIGH-CONTENT TABLETS			
<b>(57) Abstract</b>  The present invention provides a novel formulation of matter and a novel process for making it. In particular, the present invention provides unique and novel 1000 mg tablets of Colestipol hydrochloride having the advantageous properties of hardness and low friability and a novel process for making such tablets.			

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## COLESTIPOL HYDROCHLORIDE HIGH-CONTENT TABLETS

### DESCRIPTION

#### BACKGROUND OF THE INVENTION

The present invention provides a novel formulation of matter and a novel process for making it. In particular, the present invention provides unique and novel high potency (e.g. 1000 mg) tablets of colestipol hydrochloride having the advantageous properties of hardness, friability and thickness, and a novel process for making such tablets.

Colestipol is a basic anion exchange resin described as a high molecular weight copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane (hydrochloride), with approximately 1 out of 5 amine nitrogens protonated. It may also be named as diethylenetriamine-epichlorohydrin copolymer, hydrochloride. It is a light yellow resin which is hygroscopic and swells when placed in water or aqueous fluids. See Merck Index (Tenth Edition) #2440, page 2438. Colestipol hydrochloride is commercially available in granule form as COLESTID® Granules. See Physicians Desk Reference (PDR) 42nd Ed., p. 2119 (1988).

COLESTID® Granules are marketed as a hyperlipidemia agent for oral use. COLESTID® Granules are tasteless and odorless, although they may have a pronounced gritty texture when suspended in liquids consumed orally.

Cholesterol is the major, and probably the sole precursor of bile acids. During normal digestion, bile acids are secreted via the bile from the liver and gall bladder into the intestines. Bile acids emulsify the fat and lipid materials present in food, thus facilitating absorption. A major portion of the bile acids secreted is reabsorbed from the intestines and returned via the portal circulation to the liver, thus completing an enterohepatic cycle. Only very small amounts of bile acids are found in normal serum. Physicians' Desk Reference (P.D.R.) 42nd Edition, 1988, page 2115.

Colestipol hydrochloride, sold, e.g., in COLESTID® Granules, is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins). These granules must be consumed orally and typically require admixture with a pleasant tasting vehicle at the time of oral consumption. The typical daily dose of COLESTID® Granules employed for anti-hypercholesterolemia varies from 15 to 30 grams per day. Patients taking this medication ordinarily must continue to take anti-cholesterolemic drugs throughout their lives to maintain reduced serum cholesterol levels.

However, COLESTID® Granules, are not well tolerated by patients since the gritty texture of the product is objectionable, severely compromising the pharmaceutical elegance and patient acceptance. Further, the use of a granule formulation means that drug must be mixed with a liquid vehicle at the time of consumption, an inconvenience for many patients. For

example, in order to take this drug, patients must measure the powder, disperse it in a liquid vehicle and drink the entire contents. Therefore, a pharmaceutically more elegant and convenient dosage form of Colestipol hydrochloride is needed, such as a tablet.

#### INFORMATION DISCLOSURE

- 5 U.S. Patent Application, Serial Number 07/623,904, filed December 19, 1990, (which is also International Publication No. WO 89/12452, published 28 December 1989) discloses fine-milled colestipol hydrochloride and tablets made therefrom. Some of the differences between these tablets and the tablets of the current invention are listed in Table 1. Table 2 shows some of the differences between the processes used to make these two different tablets.
- 10 According to Table 1, the tablets of the present invention are much harder than the prior art tablets, yet they disintegrate readily. Also, the tablets of the present invention are advantageously smaller than the prior art tablets. Other advantageous properties of the tablets of the present invention, such as friability and disintegration time, are also set forth in the Table.
- 15 According to Table 2, the process of the present invention utilizes a wet granulation method at the bulk drug stage rather than direct compression, thus avoiding repetitive drying of the material. The present process utilizes a one-step drying process whereas the prior art utilizes a two-step drying process. These and other differences are further exemplified below.
- 20 Pharmaceutical Dosage Forms: Tablets, Volume 1, Edited by H.A. Lieberman and L. Lachman (1980), Marcel Dekker, Inc., New York and Basel, pp. 114-116, 122-129, 184-185, includes a description of the wet granulation process which is a well known method for preparing granules for tableting. It is stated that it is the process of choice to use in tablet formulations of many high-dose drugs. It also describes a number of excipients such as binders, which are used in a tablet formulation in addition to the active ingredient. It lists the
- 25 following as binders that are used in wet granulation: starch, pregelatinized starch, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone and polyvinyl alcohols. It states that the binder is fundamental to the granulation particle size uniformity, adequate hardness, ease of compression and general quality of the tablet.
- 30 Polyvinyl pyrrolidone, also known as PVP and Povidone, is a well known tablet binder and granulating excipient. USP XXII (1990) "Povidone" on page 1118.
- Published European application 0 347,748 discloses a composition for coating drug granules which is made of a polymer, such as povidone, and microcrystalline cellulose. It states the belief that the polymer material functions as a binder and carrier for the
- 35 microcrystalline cellulose, while the microcrystalline cellulose imparts the excellent compressibility properties to the granules.

Remington's Pharmaceutical Sciences, RPS XIV, John E. Hoover, Managing Editor, 14th Edition, (1970) Mack Publishing Co, Pa., pp. 1655-1659 describes the different steps and equipment that may be used in wet-granulation method for tablet preparation.

5        Colestipol hydrochloride in the form of spherical beads, wherein at least 75% of the particles by weight or volume are greater than 100 microns in diameter and 30% of the particles by weight or volume are greater than 80 microns in diameter, is known. See PDR, supra, page 2115. The use of oral colestipol hydrochloride formulations in spherical bead form to treat hypercholesterolemia is also known. See, e.g., U.S. patent 3,692,895.

10        A fine-beaded form of Colestipol hydrochloride is disclosed in International Publication WO 90/02148, published 8 March 1990.

U.S. Patent 4,404,346 discloses and claims a process for reducing the size of particles of anti-hypercholesterolemic cholestyramine resins. Powdered cholestyramine resin is produced by swelling or shrinking resin particles by contact with water or an organic solvent to introduce strain within the particles and comminuting the swollen or shrunk particles by grinding them in  
15        a rotary attrition mill. Particle sizes such that 90% by weight and/or number is below 30 microns in average particle diameter in the wet swollen state are reported to have been achieved.

EP-B-0026574, claims a process for reducing the size of particles of synthetic polymeric ion exchange or adsorbent resins in general, and of cholestyramine specifically. It also  
20        claims the comminuted synthetic polymeric ion exchange or adsorbent resin obtained by this process, the comminuted cholestyramine obtained by this process, and the resins themselves in pharmaceutical formulations.

U.S. Patent 3,692,895 claims a method of using colestipol hydrochloride to reduce hypercholesterolemia in humans. It discloses compositions (including tablets and capsules) and  
25        processes for reducing hypercholesterolemia in affected mammals and birds. The compositions and processes utilize an orally effective amount of a non-toxic polymer prepared from a polyethylenepolyamine such as tetraethylenepentamine and a bifunctional substance such as epichlorohydrin or 1,2:3,4-diepoxybutane.

U.S. Patent 4,439,419 discloses a method of using colestipol hydrochloride to  
30        neutralize gastric acidity and treat hyperacidity in humans having an excess of gastric acidity and the treatment of ulcers.

A preferred method for preparing colestipol hydrochloride for medical use is disclosed in U.S. Patent 3,803,237 and is known as the "bead process." U.S. Patent 4,631,305 claims compressed tablets containing a polymeric material such as colestipol hydrochloride as a tablet  
35        disintegrating agent.

#### SUMMARY OF THE INVENTION

The present invention particularly provides:

A pharmaceutical tablet, which comprises:

- a) one or more pharmaceutically acceptable excipients, and
  - b) an amount of colestipol hydrochloride effective to treat or prevent hypercholesterolemia in a patient to whom one or more tablets are administered;
- which has the following physical characteristics:

Hardness: 40 - 75 SCUs

Thickness: 0.200" - 0.340"

Friability: 0 - 0.1% /15 minutes; and

- 10 A process for preparing a 1000 mg tablet of colestipol hydrochloride which comprises: adding povidone to a slurry of fine milled colestipol hydrochloride.

By "Hardness" is meant the measure of the force needed to fracture a tablet when such tablet is placed lengthwise on the Hardness Tester. It is measured in Strong Cobb Units (SCUs).

- 15 The "Friability" is the measure of the stability of the tablet needed to sustain the rolling action of a coating pan and packaging. It is measured at timed intervals, such as 15 minutes, in a Roche Friabulator.

By "Thickness" is meant the measure of the height of the tablet in inches, using a micrometer.

- 20 The "Disintegration Time" is the time necessary for the tablet to break apart in purified water (37°C). It is measured in minutes.

- By a "Slurry of Fine Milled Colestipol Hydrochloride" is meant a mixture of Colestipol hydrochloride beads and water, at a ratio of from 5 to 1 (water to beads) to a ratio of 12 to 1 (water to beads), which has been milled in a precision incremental cutting machine, such as a Comitrol mill, according to the process described in International Publication No. WO 89/12452, published 28 December 1989, which is hereby incorporated by reference herein. The Colestipol hydrochloride beads are prepared by the "bead process" which is described in U.S. Patent 3,803,237, which is hereby incorporated by reference herein, and may be utilized in the slurry in a dried state (e.g., Formula B-3 material in Chart B) or in a wet state (e.g., Formula A-3 material in Chart A), with the wet state being preferred. The beads may also be prepared by the "fine bead process" which is described in International Publication No. WO 90/02148, published 8 March 1990, which is hereby incorporated by reference herein.

- 35 By "fine milled" is meant a substantially non-spherical form of colestipol hydrochloride (greater than 95% non-spherical, fractured particles, most preferably greater than about 99% non-spherical fractured particles) wherein greater than 75% of the particles by weight or volume are less than about 100 microns in diameter; more preferably greater than about 75% of

the particles, by weight or volume, are less than about 65 microns in diameter and greater than about 30% of the particles (as a proportion of their total weight or volume), are less than about 30 microns in diameter. These measurements of diameter of particle size may be made by standard light scattering assay techniques. The "fine milled" form of colestipol hydrochloride is also described in International Publication No. WO 89/12452, published 28 December 1989, as noted above.

By "Dewatered" is meant that water has been removed from the slurry by known conventional processes, down to a moisture content of 74 - 85%, and preferably 80%.

The preferred amount of colestipol hydrochloride per tablet of the present invention is 1000 mg. In hyperlipidemic patients with serum cholesterol values above 200 mg per 100 ml, the tablets of the present invention have been shown to effectively lower cholesterol levels. Current clinical data shows that two 1000 mg tablets administered to such patients twice daily lower cholesterol approximately 12% and eight 1000 mg tablets administered to such patients twice daily lower cholesterol approximately 24%.

The tablets of present invention also typically have the following additional physical characteristics: Tablet Weight: 1017 mg - 1079 mg; and Disintegration Time: Less than 5 minutes. The tablets may be compressed and preferably have a tablet weight of approximately 1048 mg, a hardness of 40 to 50 SCUs, and a thickness of 0.320" - 0.340".

The excipients which are preferred for use in the tablets of the present invention are povidone, colloidal silicon dioxide and magnesium stearate. The amounts of these excipients in the tablets of the present invention are from about 10 to about 200 mg of povidone, from about 1 to about 50 mg of colloidal silicon dioxide, and from about 1 to about 30 mg of magnesium stearate. The preferred amounts of these excipients are from about 40 to about 50 mg of povidone, from about 5 to about 10 mg of colloidal silicon dioxide, and from about 2.5 to about 3.5 mg of magnesium stearate, with approximately 40 mg of povidone, approximately 5 mg of colloidal silicon dioxide and approximately 3 mg of magnesium stearate, being most preferred.

The tablets of the present invention may further have a seal coating comprising cellulose acetate phthalate and triacetin. The amounts of these ingredients in the seal coating are from about 2 to about 100 mg of cellulose acetate phthalate and from about 0.5 to about 20 mg of triacetin, with approximately 15.6 mg of cellulose acetate phthalate and approximately 3.12 mg of triacetin, being most preferred.

The tablets of the present invention may also have a clear coating, in addition to the seal coating, comprising hydroxypropyl methylcellulose and triacetin. The amounts of these ingredients in the clear coating are from about 5 to about 100 mg of hydroxypropyl methylcellulose 2910 E5 Premium USP 5 CPS, from about 5 to about 100 mg of

hydroxypropyl methylcellulose 2910 USP 15 CPS and from about 2 to about 80 mg of triacetin, with approximately 30 mg of hydroxypropyl methylcellulose 2910 E5 Premium USP 5 CPS, approximately 30 mg of hydroxypropyl methylcellulose 2910 USP 15 CPS and approximately 12 mg of triacetin, being most preferred.

- 5           Tablet coating is designed to maintain structural integrity when exposed to the humid air and will not delay disintegration time significantly. This produces a stable dosage form.

The finished film coated tablets of the present invention typically have the following physical characteristics: Tablet Weight: 1100-1230 mg; Disintegration Time: Less than 30 minutes; Hardness: Greater than 60 SCUs; Thickness: 0.200" - 0.400"; Friability: 0 - 0.1%  
10 /15 minutes. Preferably, these tablets have a tablet weight of approximately 1138 mg, a hardness of 70 - 80 SCUs, a thickness of approximately 0.375", and a friability of approximately 0% /15 minutes.

Povidone, a binder, is usually added during the wet granulation stage rather than the bulk drug stage, as is done in the present invention. This eliminates a rewetting/drying step  
15 which saves time and money. While not intending to be limited by theory, it is believed that adding Povidone, according to the process of the current invention, may increase the cohesiveness of the colestipol hydrochloride molecules, which have two basic bonds, inter- and intra- forces. The addition of Povidone in the Colestipol hydrochloride manufacturing process may increase the cohesiveness of the inter- and intra-molecular bonds due to the nature of the  
20 polymeric structure. From about 10 to about 200 mg of Povidone may be used in the process of the current invention, with 40 mg being preferred.

Other pharmaceutical binders which will work in the process of the current invention include hydroxymethyl cellulose, hydroxyethyl cellulose and starch. However, Povidone is preferred.

- 25           Chart A shows the process of the current invention which utilizes a one-step drying method including wet granulation of the bulk drug. Chart B shows an alternate method of wet granulating the tablets which utilizes a two-step drying process similar to what is found in pharmaceutical manufacturing of granulated tablets. Tablets of the present invention were manufactured using both methods and it was found that Chart A is much more efficient than  
30 Chart B.

#### CHART A

Chart A describes the preferred method for preparing a film coated 1000 mg tablet of Colestipol hydrochloride.

- 35           The compounds A-1 and A-2 are polymerized and crosslinked according to the process described in U.S. Patent 3,803,237, which is hereby incorporated by reference herein. Water is added to the resulting material at a ratio of 5 parts water to 1 part resulting material to a

ratio of 12 parts water to 1 part resulting material to give a Colestipol hydrochloride slurry (A-3). A ratio of 12 parts purified water USP to one part resulting material is preferred. The slurry is milled with a precision incremental cutting machine, such as a Comitrol mill to yield milled Colestipol hydrochloride slurry (A-4) having approximately 92% moisture. The milled  
5 slurry is dewatered to give milled dewatered Colestipol hydrochloride (A-5) having approximately 80% moisture. A binder Povidone USP K = 30 is added to the milled dewatered Colestipol hydrochloride at a level of 4% to give milled, dewatered Colestipol hydrochloride with povidone (A-6). The wet granulated material is passed through a dryer, such as a Wyssmont Dryer or an Inox Vacuum Dryer, until loss on drying (LOD) is below 1%  
10 moisture to give dried milled Colestipol hydrochloride aggregates with povidone (A-7). The use of the Inox Vacuum Dryer is preferred. This material is then deaggregated using a Micropulverizer with an 046 screen, or other suitable mill, such as a Comil, to break up any aggregate-clumps formed during drying. Colloidal Silicon Dioxide NF is added as a glidant and anti-caking agent, and Magnesium Stearate is added to lubricate the stock. The resulting  
15 material is compressed into a tablet using a D tooling press (8,000 - 10,000 lbs compressional force) to give compressed tablets (A-8).

A seal coating is placed on the tablet consisting of Cellulose Acetate Phthalate NF (CAP), which is dissolved in a mixture of Methylene Ketone (MEK) and S.D. Alcohol 3A Anhydrous, to give seal coated tablets (A-9). Triacetin USP is used as the plasticizer for the  
20 CAP solution. This sealing solution provides a barrier which allows the aqueous clear coating to be applied to the surface of the tablet without initiating disintegration of the tablet core upon contact.

An aqueous clear coating is placed on the tablet consisting of Hydroxypropyl Methylcellulose E5 Premium 2910 USP 5 CPS and 15 CPS to give clear coated tablets (A-10).  
25 The solids for the clear coating are dissolved in Purified Water USP, using Triacetin USP as the plasticizer. This clear coating gives the tablets the strength to withstand swelling from exposure to humid environmental conditions.

Finally, the tablet is waxed with Carnauba Wax NF #120 for ease in packaging to give a film coated 1000 mg tablet of Colestipol hydrochloride (A-11).

### 30 CHART B

Chart B describes an alternative method for preparing a film coated 1000 mg tablet of Colestipol hydrochloride of the present invention.

The compounds B-1 and B-2 are polymerized and crosslinked according to the process described in U.S. Patent 3,803, 237, which is hereby incorporated by reference herein. The  
35 resulting material is washed with water at a ratio of 8 parts Purified Water USP to one part resulting material and then dried to less than 1% moisture to give Colestipol hydrochloride USP

- (B-3). (See, e.g., the "bead process" disclosed in U.S. Patent No. 3,803,237.) Water is added to the Colestipol hydrochloride USP at a ratio of 5 parts water to one part Colestipol hydrochloride USP to a ratio of 12 parts water to one part Colestipol hydrochloride USP. A ratio of 12 parts purified water USP to one part Colestipol hydrochloride USP is preferred.
- 5 The Colestipol hydrochloride USP and water are then mixed to give Colestipol hydrochloride slurry (B-4). The slurry is milled with a Comitrol mill to yield milled Colestipol hydrochloride slurry (B-5). This slurry is then dewatered with a Buchner funnel to yield milled, dewatered Colestipol hydrochloride (B-6). This material is then tray dried down to 20% moisture to give milled, semi-dried Colestipol hydrochloride (B-7). (See, e.g., the process disclosed in
- 10 International Publication No. WO 89/12452, published 28 December 1989.) This material is placed in the product container of a GLATT Fluid Bed Processor. Povidone solution is sprayed into the GLATT to produce Colestipol hydrochloride granules with Povidone (B-8). These granules are dried, in the GLATT, until the outlet temperature reaches approximately 60°C, producing dried milled, granulated, Colestipol hydrochloride Aggregates with Povidone (B-9).
- 15 This material is then deaggregated using a Micropulverizer with an 046 screen, or other suitable mill, such as a Comil, to break up any aggregate-clumps formed during drying. Colloidal Silicon Dioxide NF is added as a glidant and anti-caking agent, and Magnesium Stearate is added to lubricate the stock. The resulting material is compressed into a tablet using a Manesty Express with D tooling to yield compressed tablets (B-10).
- 20 The compressed tablets are seal coated (B-11), clear coated (B-12) and waxed, as described in Chart A above, to give film coated 1000 mg tablets of Colestipol hydrochloride (B-13).

Colestipol hydrochloride is a crosslinked polymer. The compound will swell to three to four time of its volume in the aqueous phase. If colestipol hydrochloride is compressed into a

25 tablet without a binder, the tablet will not attain the hardness needed to withstand coating and shipping. Friability of such a tablet must be below 0.1% in 15 minutes and the tablet thickness must be less than 0.340". The tablets of the current invention, surprisingly and unexpectedly, have these advantageous properties as detailed in the examples below.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

##### 30 EXAMPLE 1 Colestipol Hydrochloride - 1000 mg Tablet (Refer to Chart A)

###### 1. Process A: 1) Slurry preparation (mixing - milling - dewater)

###### Slurry preparation:

Colestipol hydrochloride beads	300 Kg
Purified Water USP	3600 Kg

- 35 MIXING- In a suitable container, mix the above for about 30 min. to about 1 hour or until the mixture is hydrated.

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**MILLING-** Pass the above mixture through a Comitrol 1700 mill.

**DEWATER-** Pass the milled material through a Sharple Centrifuge.

Total yield after dewater approx 1620 Kg (82% moisture content)

2. **Process B: PVP adding**

5 **PVP Solution Preparation:**

Povidone (PVP) 12 Kg

Purified Water USP 36 Kg

**PREPARATION:** To a suitable container mix the above until solution is clear.

10 **MIXING:** To a Pony mixer, add 405 Kg milled dewatered Colestipol and 12 Kg Povidone Solution (25%). Mix for 5 minutes.

3. **Process C: Drying**

When using a Wyssmont Dryer, predry the material with the following parameters:

15 1) Inlet temperature 230°F  
2) Total feeding time 12 hrs  
3) Outlet temperature no reading  
4) Residence time 3 1/2 hrs  
5) Final moisture 20%

Then pass the material through #8 screen and dry under the following conditions:

20 1) Inlet temperature 190°F  
2) Total feeding time 5 hrs  
3) Residence time 1 1/2 hrs  
4) Final moisture 0.2%  
5) Water soluble content 0.1%

When using an Inox Vacuum Dryer, dry the material with the following parameters:

25 1) Inlet temperature 120-160°C  
2) Vacuum 22-25 millibar  
3) Maintain product temperature at less than 50°C  
4) Endpoint loss on drying (LOD) is less than one percent (1%).

4. **Process D: Deaggregation (micropulverizing)**

30 Pass the batch through a micropulverizer (or other suitable deaggregation device) with herring bone shape screen size 046.

5. **Process E: Mixing**

To a 5 cu ft PK Blender add:

35 Dried milled Colestipol hydrochloride 50 Kg  
Cab-o-sil 250 g  
Magnesium Stearate 150 g

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Mix for 10 minutes and 3 minutes respectively.

6. Process F: Compressing

Compress the mixture from step 5 on a Manesty Express with Motrin 800 mg D tooling (0.7446" x 0.378" special capsule elliptical), using a Compression force of 8,000 - 10,000 lbs.

The physical characteristics initially measured for the compressed tablets were typically as follows: (The figures are approximate)

	Disintegrating time (for 6 tablets)	4 minutes 53 seconds
	Tablet thickness	0.327"
10	Tablet hardness	43.7 SCUs
	Tablet weight	1046 mg
	Friability	0 - 0.1%/15 minutes

7. Process G: Seal coating

	Per Tablet		Per 100 Kg batch
15	1048 mg	Compressed Tablet Cores	103 Kg
	15.6 mg	Cellulose Acetate Phthalate NF	1.544 Kg
	120 mg	Methyl Ethyl Ketone	11.88 Kg
	120 mg	S.D. Alcohol 3A Anhydrous	11.88 Kg
	3.12 mg	Triacetin USP	308.9 g

20 To a suitable container, mix the above ingredients until the solution is clear and lump free. Spray the solution on the batch with the Accela-Cota 48" by the following parameters:

	Inlet temperature	15-30°C
	Exhaust temperature	
	a. begin	Room Temperature
25	b. during	Room Temperature
	Spray rate	430 g/min
	Airless (Graco) gun pressure	20-40 lbs
	Pan Speed	5 RPM's

8. Process H.: Clear Coating

30	Per Tablet		Per 100 Kg batch
	1066 mg	Sealcoated Colestid Tablets	105 Kg
	30 mg	Hydroxypropylmethyl Cellulose E5 Premium 5cps	2.97 Kg
	30 mg	Hydroxypropylmethyl Cellulose 15cps	2.97 Kg
35	12 mg	Triacetin USP	1.188 Kg
	860 mg	Purified Water USP	85.14 Kg

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Mix the above ingredients until solution is clear. Spray the solution on the tablets in Accela-Cota 48" according to the following parameters:

	1. Inlet temperature	80-85°C
	2. Outlet temperature	
5	a. begin	45°C
	b. during	40-45°C
	3. Air Atomization	
	a. nozzle	50 psi
	b. cylinder	70 psi
10	4. Spray rate	660 g/min
	5. Binks gun air spray system	4 GUNS
	6. Disintegration time	NMT 10 min

The physical characteristics of the final film coated tablets were typically as follows:

(The figures are approximate)

15	Weight:	1138 mg
	Disintegration Time:	less than 30 minutes
	Hardness:	60 - 80 SCUs
	Thickness:	0.375"
	Friability:	0%/15 minutes

## 20 EXAMPLE 2 1000 mg Colestid Tablets (Refer to Chart B)

Wet 7 kg of Colestipol hydrochloride USP with 84 Liters of Purified water USP in a suitable container and mix until dispersed. Using a Comitrol Mill, wet mill the Colestipol hydrochloride to achieve a reduced particle size. Dewater the milled slurry using a Buchner funnel and place on Trays to dry to 20% moisture. Using the following formula and methods,

25 compress into a tablet which can be film coated:

Colestipol hydrochloride, milled (20% moisture) 7 Kg

Granulation excipient preparation:

PVP 280 g

Water/ethanol, 1/1 1100 g

30 Dissolve PVP into water/alcohol mixture with agitation. To the Product container, add the Colestipol hydrochloride. Granulate with the PVP solution according to the following parameters:

	Inlet temperature	90°C
	Outlet temperature	40°C
35	Spray rate	8-70 Gm/min

Final dry to outlet temperature of at least 50°C

## Final mixing:

Colestipol granules from above	1 Kg
Ca-bo-sil	5 g
Magnesium Stearate	3 g

- 5 Directions: Mix the above ingredients in a Hobart Mixer for 5 minutes.

Compress the mixture into tablet using a Manesty Express with D tooling, (0.7446" x 0.378" special capsule elliptical) using a 8,000 - 10,000 lbs compressional force.

- 10 The physical characteristics initially measured for the compressed tablets were typically as follows: (The figures are approximate)

Disintegration time: (6 tablets):	5 minutes
Weight:	1056 mg
Hardness:	43.7 SCUs
Thickness:	0.329"
15 Friability:	0% /4 min.; < 0.1 %/15 min.

The ingredients listed in Table 3 below are used to coat the tablets.

The following parameters are used to seal coating: (24" Accela-Cota)

Inlet air temperature:	15-30°C
Outlet air temperature:	15-30°C
20 Air flow rate: nozzle: 30	psi cylinder: 60 psi
Spray rate:	20-35 RPM's
Pan Speed:	12-20 RPM's

The following parameters are used for the clear coating: (24" Accela-Cota)

25 Inlet air temperature:	Adjust to maintain outlet air
temperature Outlet air temperature:	40-50°C
Air atomization pressure: nozzle: 30	psi cylinder: 60 psi
Pan Speed:	12-20 RPM's
Binks guns	1 air Binks gun

Wax the coated tablets with Carnauba wax NF for ease in handling.

- 30 The physical characteristics of the final film coated tablets are given in Example 1.

## EXAMPLES 3-18 Failure of Other Tablets

- The following examples demonstrate attempts at making a 1000 mg Colestid Tablet, which were unsuccessful for tableting and/or coating. The formulation used, the physical characteristics obtained, and in some examples, the process steps used, are given. These failures demonstrate the surprising and unexpected results achieved by the tablets and process of the current invention.
- 35

**EXAMPLE 3**

Formulation was as follows:

Colestipol hydrochloride (milled) 1 Kg

Magnesium Stearate 5 g

5 Weigh ingredients and mix well using a Hobart mixer.

Physical characteristics were as follows: (Kilian press)

Weight: 1005 mg

Disintegration: 3" 55'

Hardness: 41.2 - 44.1

10 Thickness: 342 - 372"

Friability: 4.92814%

Pressure: 4,400 lbs

Precomp. Pressure: 400 lbs

15 These tablets had friability and flow problems. With these tablets, it was not possible to achieve the desired tablet weight.

**EXAMPLE 4**

Excipients for granulation were as follows:

Povidone k=30 (PVP) 300 g

S.D. Alcohol 3A Anhydrous 2000 ml

20 Formulation was as follows:

Colestipol hydrochloride (milled) 6 Kg

Silicon dioxide -

Magnesium Stearate 30 g

25 Weigh all materials. Mix the excipients and granulate the Colestipol using the T.K. Fielder High Sheer Mixer/Granulator. Place granulation (wet) in the ovens at 120 degrees F for 12-16 hours until dry. Lubricate with magnesium stearate. Compress on the Kilian press.

These tablets had friability and flow problems. With these tablets, it was not possible to achieve the desired tablet weight.

**EXAMPLE 5**

30 Formulation was as follows:

Colestipol hydrochloride (milled) 1 Kg

Magnesium Stearate 3 g

Avicel PH 102 30 g

Physical characteristics were as follows: (Kilian press)

35 Weight: 1030 mg

Friability: 0.149% (poor)

These were soft tablets which had poor friability and flow.

#### EXAMPLE 6

Formulation was as follows:

Colestipol hydrochloride (milled) 1 Kg

5 Magnesium Stearate 2.5 g

Physical characteristics were as follows: (Kilian Press)

Weight: 1002.5 mg

Friability: 0.97%

These tablets were not hard enough for coating pan due to poor friability.

#### 10 EXAMPLE 7

Formulation was as follows:

Colestipol hydrochloride (milled) 5 Kg

Granulation excipient:

Povidone (PVP) 300 g

15 Purified Water USP 2000 ml

Mix PVP and water until clear. Weigh 5 Kg of Colestipol hydrochloride. Heat Glatt Fluid Bed Dryer until reaches 50 degrees (going left to right on the panel) (Shaking Intervals every 30 seconds for a length of 5 seconds)

Inlet temperature: 70°C

20 Exhaust temperature: 32°C

Exhaust Air Flap: 40%

Adjust spray ratio to keep product from sticking to sides and filter.

The granulation was difficult to dry unless alcohol was used as a granulating agent.

#### EXAMPLE 8

25 Formulation was as follows:

Colestipol hydrochloride (milled) 1 Kg

Magnesium Stearate 6 g

Avicel PH 102 100 g

Physical characteristics were as follows: (Kilian Press)

30 Theory Weight: 1100 mg

Actual Weight: 650 mg

Hardness: 42.5

Pressure: 4000 lbs

Precomp: 500 lbs

35 Friability: Not measured

With these tablets, it was not possible to achieve the desired tablet weight.

-15-

**EXAMPLE 9**

Formulation was as follows:

	Colestipol hydrochloride (milled)	1 Kg
	Magnesium Stearate	6 g
5	Avicel PH 102	10 g

Screen materials and mix in a Hobart mixer.

Physical characteristics are as follows:

	Weight:	1016 mg
	Hardness:	26 - 29 SCU's
10	Friability:	0.128% (poor)
	Pressure:	2,000 - 4,100 lbs
	Precomp:	300 - 800 lbs

There was a friability problem because the tablets were too soft.

**EXAMPLE 10**

15 Formulation was as follows:

	Colestipol hydrochloride (milled)	1 Kg
	Avicel PH 102	50 g
	Magnesium Stearate	2.5 g
	Mix materials.	

20 Physical characteristics were as follows:

	Weight:	1052.5 mg
	Hardness:	33 - 34 SCU's
	Friability:	0.118% (poor)
	Pressure:	4,000 lbs
25	Precomp:	500 lbs

The friability of these tablets was not good because the tablets were too soft.

**EXAMPLE 11**

Formulation was as follows:

	Colestipol hydrochloride (milled)	800 g
30	Avicel PH 102	76 g
	Mg stearate	5 g

Physical characteristics were as follows: (Kilian Press)

	Weight:	1105 mg
	Friability:	Not measurable

35 These tablets were too soft, like a sponge, due to moisture in the Colestipol material.

**EXAMPLE 12**

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Formulation was as follows:

Colestipol hydrochloride (milled)	1 Kg
Avicel PH 102	150 g
Magnesium Stearate	6 g

5 Physical characteristics were as follows: (Kilian Press)

Weight:	1156 mg
Hardness:	36 - 44 SCU's
Friability:	Poor
Pressure:	4,400 lbs
Precomp:	550 lbs

10

Friability of these tablets was not good enough to withstand a coating pan.

#### EXAMPLE 13

Formulation was as follows:

Colestipol hydrochloride (milled)	700 g
Magnesium Stearate	4 g
Avicel PH 102	70 g

15

Physical characteristics were as follows:

Weight:	1050 mg
Hardness:	33.2 SCU's
Friability:	Poor

20

#### EXAMPLE 14

Formulation was as follows:

Colestipol hydrochloride (milled)	1 Kg
Magnesium Stearate	6 g
Avicel PH 102	100 g

25

Physical characteristics were as follows:

Weight:	1100 mg
Hardness:	42.2 - 42.7 SCU's
Friability:	0.53%

30 EXAMPLE 15

Formulation was as follows: (Kilian Press)

Colestipol hydrochloride (milled)	940 gm
Povidone (PVP)	60 g
Magnesium Stearate	2.5 g

35

Cab-o-sil	4 g
-----------	-----

Physical characteristics were as follows:

-17-

Weight: 1006 mg

The flow of these tablets was poor.

**EXAMPLE 16**

Formulation was as follows:

5	Colestipol hydrochloride (milled)	1000 g
	Povidone (PVP)	50 g
	Cab-o-sil	5 g
	Magnesium Stearate	3 g

Physical characteristics were as follows: (Kilian Press)

10	Weight:	1058 mg
	Disintegration:	5"
	Hardness:	40 SCU's
	Thickness:	0.347"
	Friability:	Average

**15 EXAMPLE 17**

Formulation was as follows:

	Colestipol hydrochloride (milled)	1000 g
	HPMC 5 CPS	50 g
	Avicel PH 102	50 g
20	Magnesium Stearate	3 g

Physical characteristics were as follows:

	Weight:	1103 mg
	Thickness:	0.356"
	Friability:	Poor

**25 EXAMPLE 18**

Formulation was as follows:

	Colestipol hydrochloride (milled)	1000 g
	Povidone (PVP)	4%
	Chilsonator	1000 lbs with a #8 screen

30 Chilsonate and fitzmill. Compress to weight.

Physical characteristics were as follows:

	Weight:	1040 mg
	Hardness:	37 - 40 SCU's
	Thickness:	0.346"
35	Friability:	Poor

TABLE 1

	Compressed Tablets of the Current Invention	Prior Art Compressed Tablets
Tablet size	0.753" x 0.382" x 0.330"	0.760" x 0.387" x 0.373"
Tablet hardness	> 40 SCUs	< 40 SCUs
Friability	0 - 0.1%/15 minutes	0.4%
Disintegration time	Less than 5 minutes	6 minutes, 50 seconds

5

TABLE 2

Process of the Current Invention	Prior Art Process
Wet Granulation method used in bulk drug manufacture to add the binder Povidone	Direct compressing of tablet excipients
One step drying by Wyssmont Dryer or Inox Vacuum Dryer	Two step drying by tray dryer

5

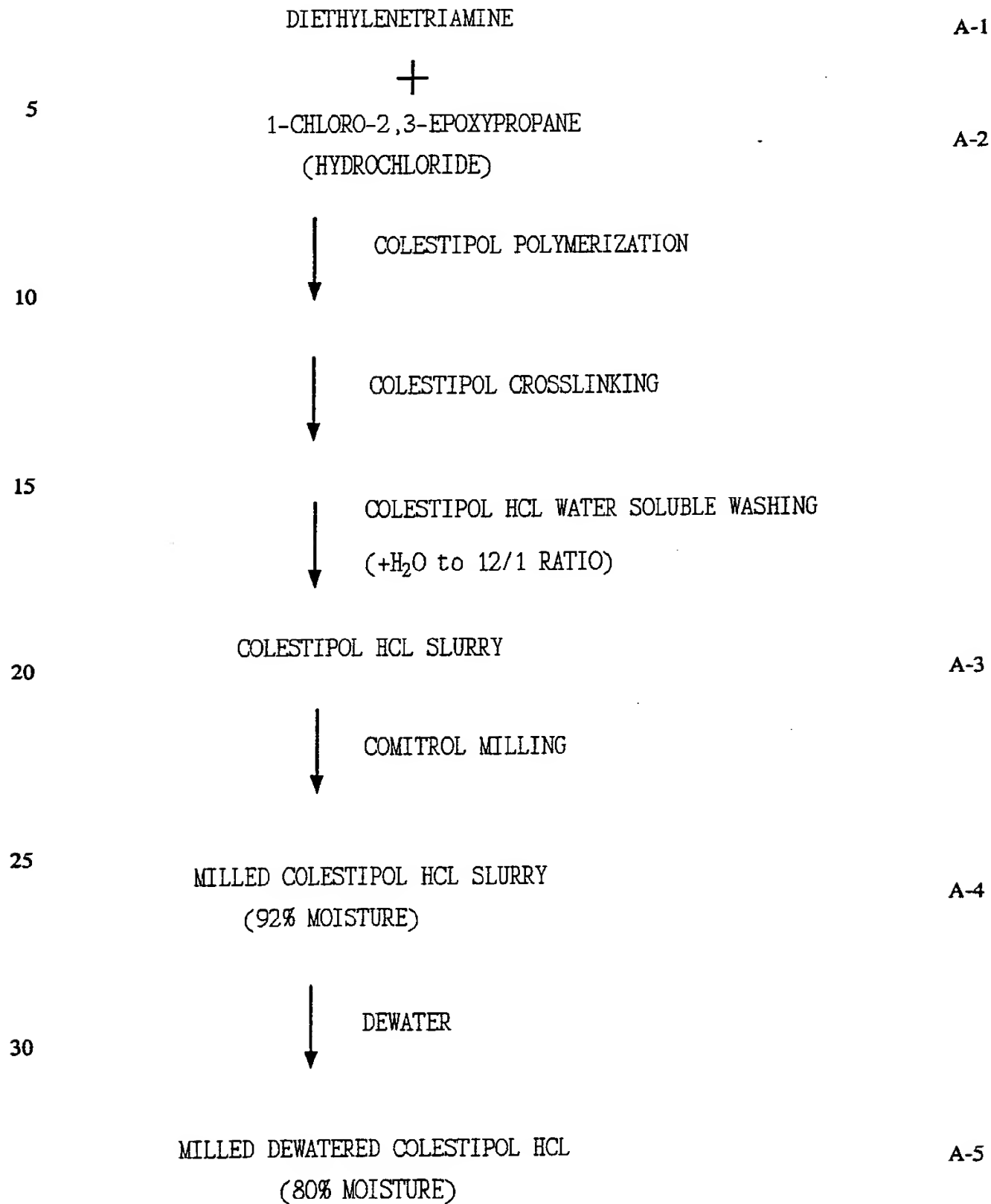
TABLE 3

Ingredients Used to Coat Tablets (Example 2)

5	PER TABLET		PER 10 Kg OF TABLETS
	15.6 mg	Cellulose Acetate Phthalate	163 g
	120 mg	Acetone or Methylethyl Ketone	1.26 kg
	3.12 mg	Triacetin USP	32.7 g
	120 mg	S.D. Alcohol 3A Anhydrous	1.26 kg
10	30 mg	HPMC E5 PREMIUM 5 CPS	314 g
	30 mg	HPMC 15 CPS	314 g
	12 mg	Triacetin USP	125.8 g
	860 mg	Purified Water USP	9 kg

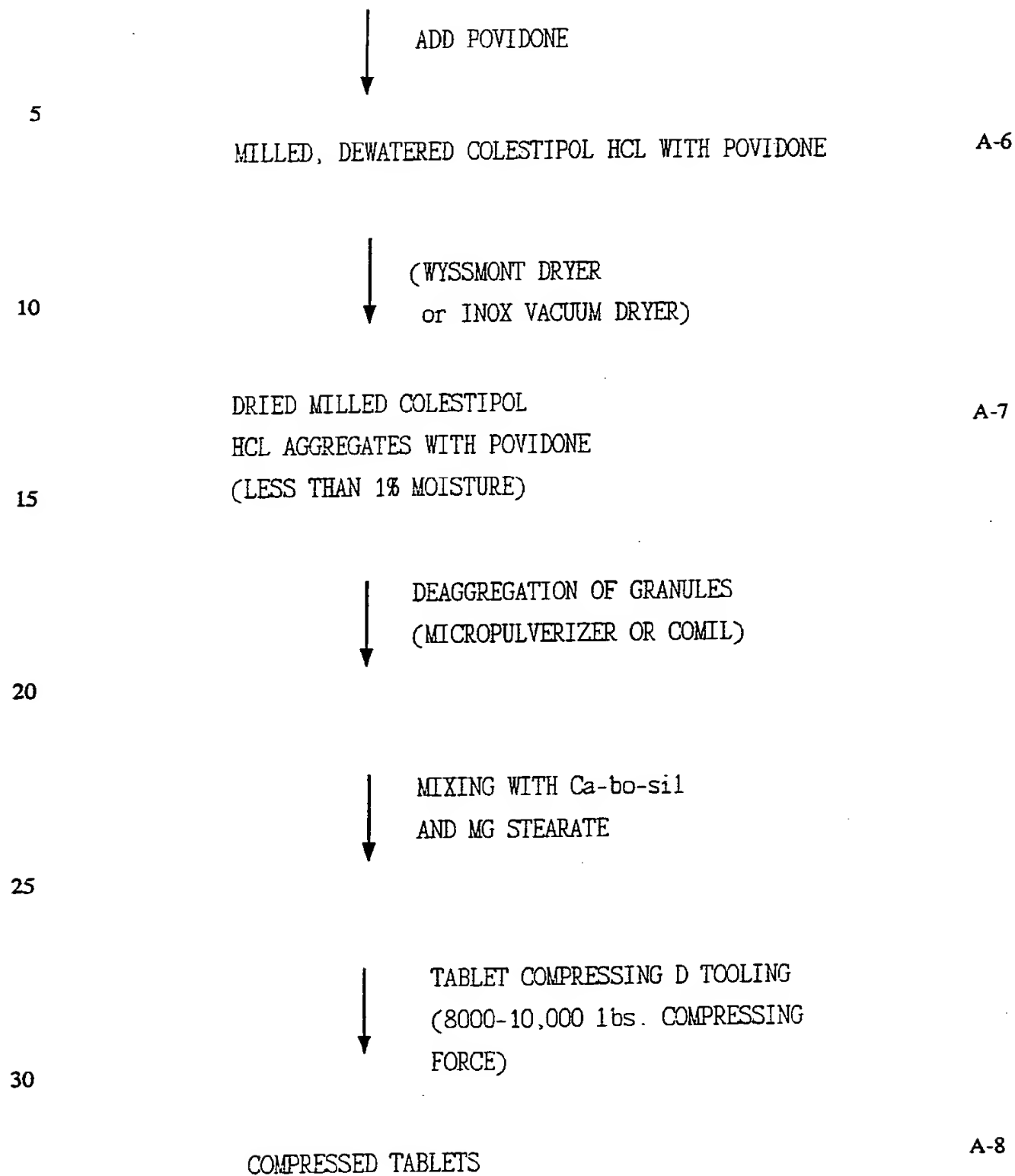
-21-

## CHART A



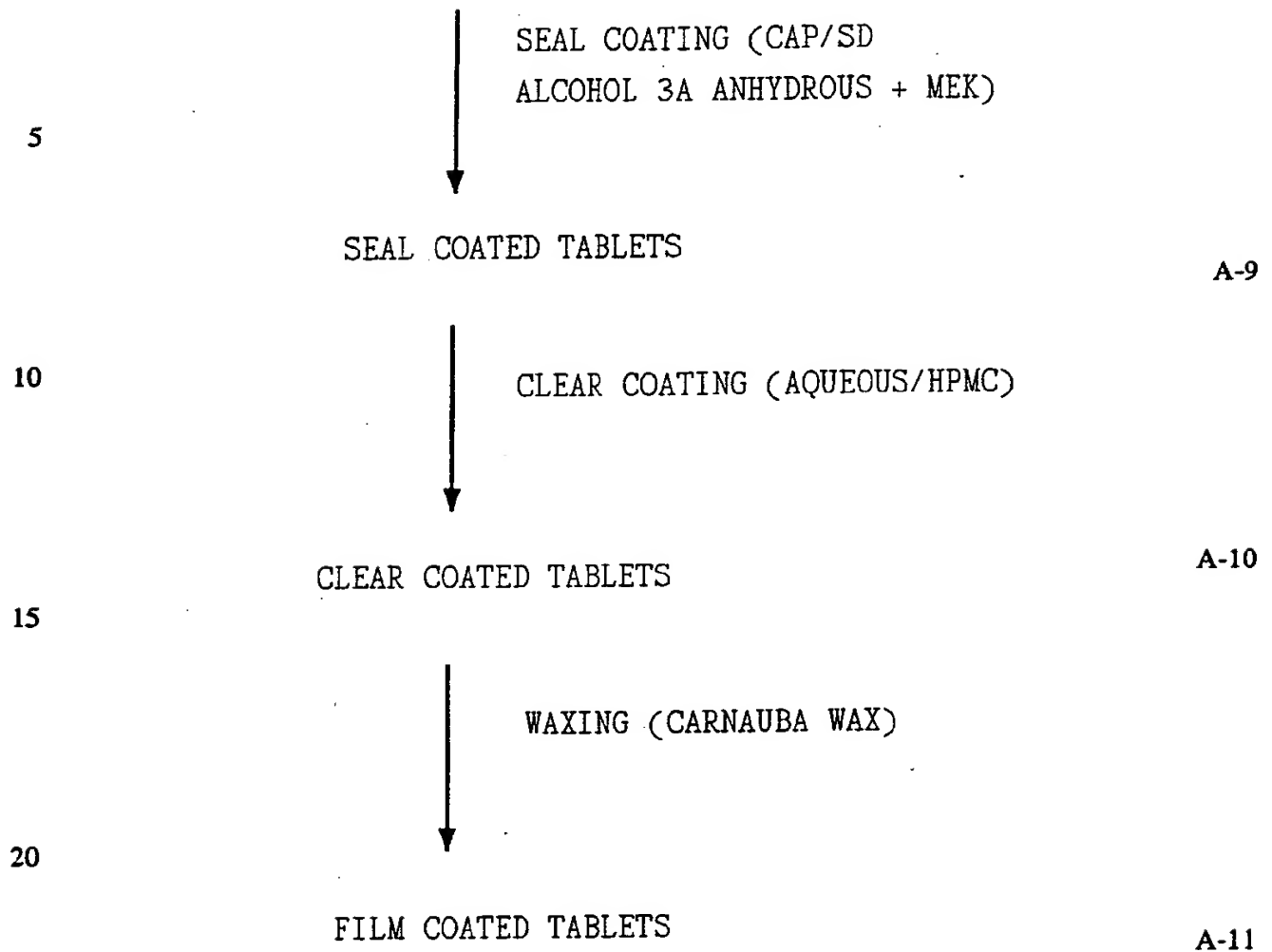
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## CHART A (continued)



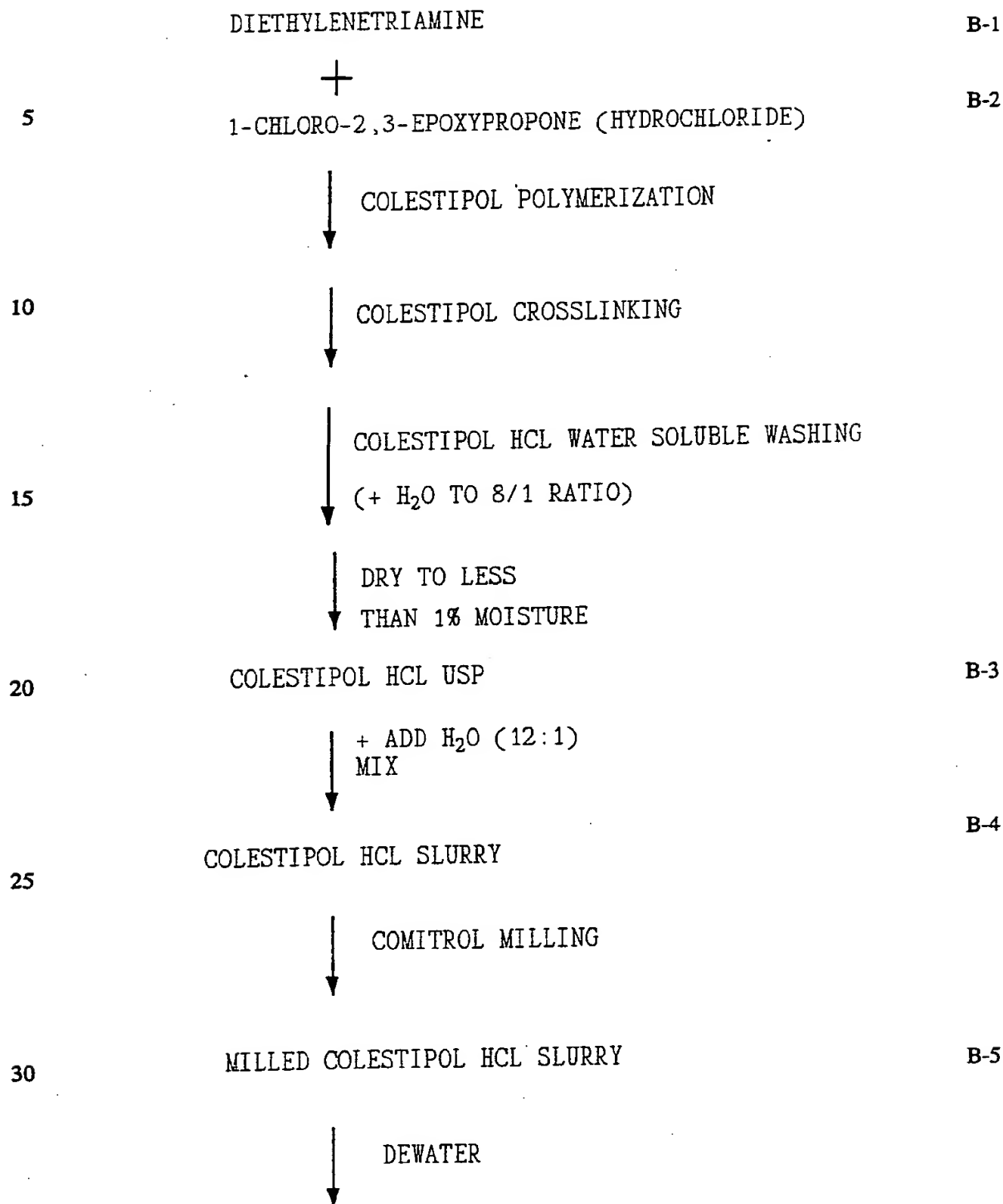
-23-

## CHART A (continued)



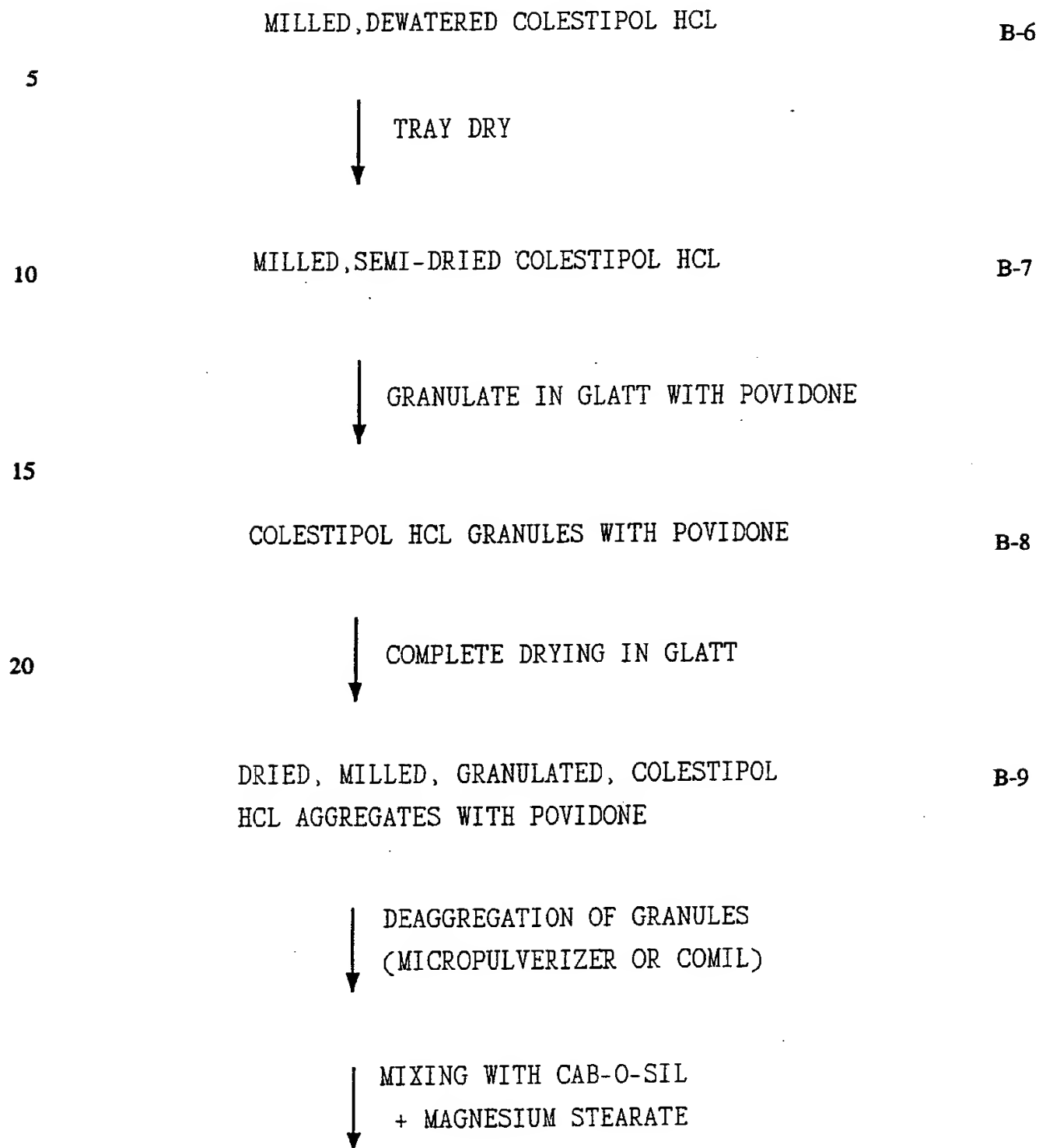
-24-

## CHART B



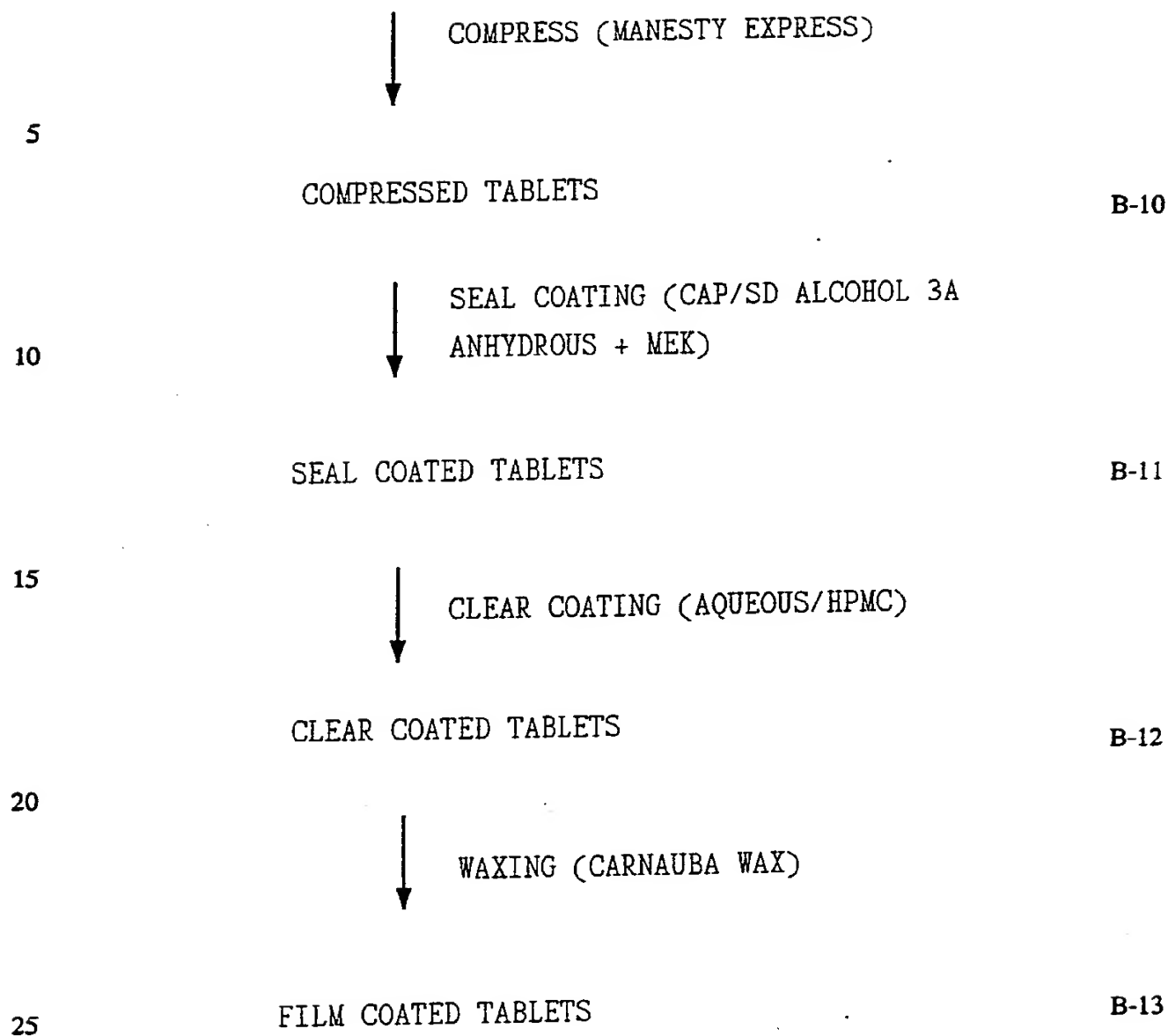
-25-

## CHART B (continued)



-26-

## CHART B (continued)



## CLAIMS

1. A pharmaceutical tablet, which comprises:
  - a) one or more pharmaceutically acceptable excipients, and
  - b) an amount of Colestipol hydrochloride effective to treat or prevent hypercholesterolemia in a patient to whom one or more tablets are administered;which has the following physical characteristics:

Hardness:	40 - 75 SCUs
Thickness:	0.200" - 0.340"
Friability:	0 - 0.1% /15 minutes.
2. The tablet of Claim 1 wherein the Colestipol hydrochloride is fine milled colestipol hydrochloride.
3. The tablet of Claim 1 which has the following additional characteristics:

Tablet Weight:	1017 mg - 1079 mg
Disintegration Time:	Less than 5 minutes.
4. The tablet of Claim 3 having approximately 1000 mg of Colestipol hydrochloride and wherein the tablet weight is approximately 1048 mg, the hardness is 40 to 50 SCUs, and the thickness is 0.320" - 0.340".
5. The tablet of Claim 1 wherein the excipients are povidone, colloidal silicon dioxide and magnesium stearate.
6. The tablet of Claim 5 having approximately 1000 mg of Colestipol hydrochloride, 10 to 200 mg of povidone, 1 to 50 mg of colloidal silicon dioxide, and 1 to 30 mg of magnesium stearate.
7. The tablet of Claim 6 having 40 to 50 mg of povidone, 5 to 10 mg of colloidal silicon dioxide, and 2.5 to 3.5 mg of magnesium stearate.
8. The tablet of Claim 7 having approximately 40 mg of povidone, approximately 5 mg of colloidal silicon dioxide and approximately 3 mg of magnesium stearate.
9. The tablet of Claim 8 which further has a seal coating comprising cellulose acetate

phthalate and triacetin.

10. The tablet of Claim 9 having 2 to 100 mg of cellulose acetate phthalate and 0.5 to 20 mg of triacetin.

5

11. The tablet of Claim 10 having approximately 15.6 mg of cellulose acetate phthalate and approximately 3.12 mg of triacetin.

12. The tablet of Claim 11 which further has a clear coating comprising hydroxypropyl methylcellulose and triacetin.

10

13. The tablet of Claim 12 having 5 to 100 mg of hydroxypropyl methylcellulose 2910 E5 Premium USP 5 CPS, 5 to 100 mg of hydroxypropyl methylcellulose 2910 USP 15 CPS and 2 to 80 mg of triacetin.

15

14. The tablet of Claim 13 having approximately 30 mg of hydroxypropyl methylcellulose 2910 E5 Premium USP 5 CPS, approximately 30 mg of hydroxypropyl methylcellulose 2910 USP 15 CPS and approximately 12 mg of triacetin.

20 15. The tablet of Claim 14 which has the following physical characteristics:

Tablet Weight	1100-1230 mg
Disintegration Time:	Less than 30 minutes
Hardness:	Greater than 60 SCUs
Thickness:	0.200" - 0.400"
Friability:	0 - 0.1% /15 minutes

25

16. The tablet of Claim 15 wherein the tablet weight is approximately 1138 mg, the hardness is 60 - 80 SCUs, the thickness is approximately 0.375", and the friability is approximately 0% /15 minutes.

30

17. A process for preparing a tablet of Colestipol hydrochloride which comprises: adding povidone to a slurry of fine milled Colestipol hydrochloride.

18. The process of Claim 17 wherein 10 to 200 mg of povidone is added.

35

19. The process of Claim 18 wherein approximately 40 mg of povidone is added.

20. The process of Claim 17 wherein the slurry has been dewatered prior to adding the povidone.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/05066

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)\*

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5                      A 61 K    31/785                      A 61 K    9/16                      A 61 K    9/20

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System

Classification Symbols

Int.Cl.5

A 61 K

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>

## III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	WO,A,8912452 (UPJOHN) 28 December 1989, see claims 1-6; page 9, example 1 (cited in the application) -----	1-5

\* Special categories of cited documents: <sup>10</sup>

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

06-10-1992

Date of Mailing of this International Search Report

29.10.92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

*Dagmar Frank*

ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.

US 9205066  
SA 62005

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on 19/10/92  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8912452	28-12-89	AU-A- 3745489	12-01-90
		EP-A- 0420875	10-04-91
		JP-T- 3501614	11-04-91
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

